REMARKS

Claims 1, 11-15, 21 and 22 have been amended to specify that the human individual being treated is an individual having glycogen storage disease type II. Support for this amendment is found throughout the Specification, including, for example, at p. 5, lines 11-13. Claims 1, 11-15 and 21 have also been amended to specify that the human acid α-glucosidase is administered periodically, at an administration interval. Claim 23 has been added to specify that the administration interval can be varied over time. Support for this amendment, and Claim 23, is found throughout the Specification, including, for example, at p. 9, line 24, through p. 10, line 5. No new matter has been added.

Claims 1-9 and 11-23 are pending.

Applicant's Invention

Applicant's invention pertains to methods of treating glycogen storage disease type II (GSD-II) (infantile, juvenile or adult-onset) in a human individual having GSD-II. In the methods, a therapeutically effective amount of acid α-glucosidase (GAA) is administered to the individual periodically (as distinguished from a one-time dose, as indicated in the Specification at p. 9, lines 26-28), at an administration interval (e.g., monthly, biweekly, weekly, twice weekly, daily). The administration interval can be varied, depending on the severity of the symptoms and the needs of the individual.

The GAA is human acid α-glucosidase (hGAA) produced in Chinese hamster ovary (CHO) cell culture. Production of GAA in CHO cell culture yields a product having glycosylation which allows significant and efficient uptake of hGAA in the desired tissues (heart and muscle) and resultant cleavage of glycogen. Applicant has successfully treated infants suffering from GSD-II, by administering hGAA to them periodically. The individuals demonstrated improvement of cardiac status, pulmonary function, muscle function, and neurodevelopment, as well as reduction of glycogen levels in tissue. Applicant is the first to demonstrate successful treatment of this genetic disease affecting heart and muscle, in children who otherwise would have died from cardiac failure by about one year of age.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner rejected Claims 1-9 and 11-22, stating that the term "regular interval" was indefinite. The claims have been amended to indicate that the GAA is administered periodically, at an administration interval. As amended, the claims specify that the GAA is administered more than once, at times separated by an interval of time (the administration interval).

The Examiner also rejected Claim 22, stating that it was unclear whether the label was with the enzyme in the composition. Claim 22 has been amended to indicate more clearly that the label is on the container.

In view of these amendments, the claims even more particularly point out and distinctly claim the subject matter which Applicant regards as his invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims under 35 U.S.C. 102(b)

In order for a reference to anticipate a claim, each and every element at set forth in the claim must be found, either expressly or inherently described, in the reference (see, e.g., M.P.E.P. §2131).

Fuller *et al.*

The Examiner rejected Claims 1-4, 9, 10 and 21 as being anticipated by Fuller *et al.*, stating that Fuller *et al.* describe treatment of Pompe's disease by administration of hGAA and that the enzyme is administered to an individual.

Fuller *et al.* describe preparation of recombinant GAA in CHO cell culture. Fuller *et al.* indicate that the recombinant GAA was taken up in two types of cells from a patient having Pompe's disease: in cultured human skin fibroblasts after exposure to the enzyme for 12 hours, as well as in cultured human muscle cells after exposure to the enzyme for 24 hours. Lysosomal glycogen in the muscle cells was cleared, following addition of recombinant GAA to the culture medium of the cells.

Fuller *et al.* do not describe administering GAA to a human individual. Although Fuller *et al.* state that they believe that the precursor GAA "will be a useful candidate for replacement therapy in GSD II patients" (p. 908, Conclusion), they do not, describe administration of GAA to

anything other than cells in culture. The cells are skin cells and muscle cells; Fuller *et al.* do not describe administration of GAA to cultured heart cells, and so cannot demonstrate treatment of cardiomyopathy. Furthermore, Fuller *et al.* do not describe administration of GAA periodically, at an administration interval. They describe only a single dose treatment of the cultured cells.

In addition, Fuller *et al.* do not describe "treatment" of disease in an individual, as that term is described in the current Specification and would be understood by one of ordinary skill in the art. Neither uptake of enzyme by cultured human fibroblasts, nor uptake of enzyme by cultured human muscle cells and subsequent processing of lysosomal glycogen in the muscle cells, both occurring in the short term (e.g., 12 to 24 hours) indicates whether administration of the GAA to a patient periodically, at an administration interval, will treat the disease (e.g., by ameliorating one or more symptoms associated with the disease, preventing or delaying the onset of one or more symptoms of the disease, and/or lessening the severity or frequency of one or more symptoms of the disease). Furthermore, Fuller *et al.* cannot describe treatment of cardiomyopathy, as set forth in Claim 21, as they do not describe administration of enzyme to heart cells.

In view of these considerations, Fuller *et al.* do not teach each and every aspect of the claimed invention: they not teach periodic administration of human α-glucosidase to a human individual at an administration interval, nor do they teach actual treatment of disease. Therefore, the claimed invention is not anticipated by the teachings of Fuller *et al.*

Rejection of Claims under 35 U.S.C. §103

Fuller *et al.*

The Examiner rejected Claims 1-7, 11-18 and 21 as anticipated by, or in the alternative, as obvious over, Fuller *et al.* The Examiner also rejected Claims 1-22 as being obvious over Fuller *et al.* The issue of anticipation has been discussed above. As discussed in detail above, Fuller *et al.* do not describe administration of GAA to a human individual, nor do they describe periodic administration of GAA at an administration interval. Furthermore, Fuller *et al.* do not describe "treatment" of disease in an individual. Thus, Fuller *et al.* do not teach each and every aspect of the claimed invention, and the claimed invention is therefore not anticipated by the teachings of Fuller *et al.* The obviousness rejections are addressed concurrently below.

There is no teaching or suggestion by Fuller *et al.* that the enzyme should be administered periodically (more than once), and at an interval. One of ordinary skill in the art, using the methods described by Fuller *et al.*, would have at most been motivated only to administer a single dose of the enzyme, and not to administer enzyme periodically, at an administration interval.

Even assuming *arguendo* that one of ordinary skill in the art attempted to treat Pompe's disease using the methods described by Fuller *et al.*, and even assuming *arguendo* that more than one dose was contemplated, the current invention would nevertheless not have been obvious, because one of ordinary skill in the art would not have known whether treatment would be successful, especially because there was no previously known treatment available for this genetic disease affecting heart and muscle. The teachings of Fuller *et al.* regarding uptake of enzyme by cultured human fibroblasts, and uptake of enzyme by cultured human muscle cells and subsequent processing of lysosomal glycogen in the muscle cells, do not provide a reasonable expectation that administration of the enzyme to a patient periodically (for more than one dose) will, in fact, treat the disease. It would not have been known whether administration of GAA to a whole individual would result in uptake of the enzyme in the desired tissues (e.g., heart, skeletal muscle). For example, neither uptake of enzyme by cultured human fibroblasts, nor uptake of enzyme by cultured human muscle, indicate whether cardiomyopathy associated with GSD-II can be treated (see, e.g., Claim 21), as there is no indication whether heart cells can uptake and utilize the enzyme. Furthermore, one of ordinary skill in the art would not have known whether administration to a whole individual, in contrast to administration to the relevant part of cells (e.g.,myocytes), for treatment to be successful.

Applicant has, for the first time, demonstrated successful treatment of this genetic disease by administration of the enzyme to a human individual. As emphasized the Declaration under 37 C.F.R. §1.132 of Dr. Yuan-Tsong Chen (the "Declaration"), the treatment of patients as described in the application was unexpectedly successful.

Furthermore, because it would not have been obvious that treatment would, in fact, result from administration of the enzyme, it would not have been possible for one of ordinary skill in the art to prepare label containing instructions for administration of a composition for treatment of glycogen storage disease type II as set forth in Claim 22. Also, it should be noted that Fuller *et*

al., do not teach or suggest use of an immunosuppressant in combination with the enzyme, nor do Fuller *et al.* suggest that reactivity of the immune system affected the results in any manner. Thus, it would not have been obvious to one of ordinary skill in the art to administer an immunosuppressant in conjunction with the enzyme.

In view of these considerations, the claimed invention would not have been obvious over the teachings of Fuller *et al.*

Bijvoet *et al.* in view of Fuller *et al.*

The Examiner rejected Claims 1-22 under 35 U.S.C. 103(a) as being unpatentable over Bijvoet *et al.* in view of Fuller *et al.*, stating that it would have been obvious to use the enzyme of Fuller *et al.* in the methods of Bijvoet *et al.* and adjust the working conditions accordingly, as well as to use an immunosuppressant or provide instructions with the enzyme. The Examiner additionally indicated that Bijvoet *et al.* do administer the enzyme to an individual, namely mice.

Bijvoet *et al.* describe production of transgenic recombinant hGAA in mouse milk; administration of a single dose of GAA to GSD-II knockout mice, and a resultant increase of enzyme activity in heart and skeletal muscle samples after two days; and the uptake of the enzyme by cultured human fibroblasts.

Bijvoet *et al.* do not describe administration of GAA to a human individual, as is contemplated by the claims. Furthermore, Bijvoet *et al.* do not describe administration of GAA periodically, at an administration interval, but rather, use a single dose. There is no teaching or suggestion by Bijvoet *et al.* that the enzyme should be administered periodically, at an administration interval. One of ordinary skill in the art, using the methods of Bijvoet *et al.*, would have at most been motivated only to administer a single dose of the enzyme, and not to administer enzyme periodically.

Furthermore, it would not have been obvious to one of ordinary skill in the art, given the teachings of Bijvoet *et al.*, that the disease could, in fact, be "treated" by administration of the enzyme periodically. Bijvoet *et al.* do not describe "treatment" of disease in a human individual. Neither uptake of enzyme by cultured human fibroblasts, nor increase of enzyme activity in knockout mice administered a single dose of the enzyme, indicates whether administration of the GAA periodically at an administration interval to a patient will, for example, ameliorate one or

more symptoms associated with the disease, prevent or delay of the onset of one or more symptoms of the disease, and/or lessen of the severity or frequency of one or more symptoms of the disease.

Assuming *arguendo* that one of ordinary skill in the art attempted to treat Pompe's disease using the methods described by Bijvoet *et al.*, one of ordinary skill in the art would not have known whether treatment would be successful. The teachings of Bijvoet *et al.* regarding uptake of enzyme by cultured human fibroblasts, and increase of enzyme activity in knockout mice administered a single dose of the enzyme, do not provide a reasonable expectation that administration of the enzyme periodically to a patient at an administration interval will, in fact, treat the disease. Bijvoet *et al.* describe increased activity in homogenized mouse heart and muscle tissue; these experiments do not indicate whether the enzyme has located to the relevant cells (e.g., myocytes), that will allow it to treat disease (e.g., by decreasing glycogen and/or decreasing symptoms). In fact, as supported by the Declaration, one of ordinary skill in the art would expect that intravenous administration of enzyme would result in the presence of the enzyme in blood stream and endothelium of blood vessels, rather than in the desired target cells.

Furthermore, even if the enzyme located to the desired cells, Bijvoet *et al.* do not demonstrate a decrease of glycogen or other correction of symptoms. Without a demonstration of correction or amelioration of symptoms, one of ordinary skill in the art would have had no way to predict whether the methods would be effective to treat human individuals.

The teachings of Fuller *et al.* do not remedy the deficiencies of Bijvoet *et al.* One of ordinary skill in the art, given the teachings of Bijvoet *et al.*, would not have been motivated to look to the teachings of Fuller *et al.* regarding enzyme produced in CHO cell culture; in fact, Bijvoet *et al.* teach away from use of enzyme produced in CHO cells: they indicate that high production costs associated with use of enzyme produced in CHO cells are a significant concern and discuss experiments designed to provide proof of principle for obtaining enzyme by other means (Bijvoet *et al.*, p. 1820, "Discussion").

Even assuming *arguendo* that the teachings of Bijvoet *et al.* were combined with the teachings of Fuller *et al.*, one of ordinary skill in the art would not have obtained the present invention. One of ordinary skill in the art, using the enzyme of Fuller *et al.* in the methods of Bijvoet *et al.*, would have been motivated only to administer a single dose of the enzyme, and not

to administer enzyme periodically at an administration interval. Furthermore, Bijvoet *et al.* do not describe "treatment" of disease in an individual. As discussed above, neither uptake of enzyme by cultured human fibroblasts, nor increase of enzyme activity in knockout mice administered a single dose of the enzyme, indicates whether administration of the GAA periodically to a patient, at an administration interval, will "treat" the patients, as there was no demonstration of decrease in glycogen or improvement of muscle or heart function. Thus, it would not have been obvious to one of ordinary skill in the art that the disease could, in fact, be successfully "treated" by administration of the enzyme of Fuller *et al.* in the methods of Bijvoet *et al.* This position is further supported by the Declaration, as described above.

Furthermore, because it would not have been obvious that treatment would, in fact, result from administration of the enzyme, it would not have been possible for one of ordinary skill in the art to prepare label containing instructions for administration of a composition for treatment of glycogen storage disease type II. Also, it should be noted that neither Bijvoet *et al.* nor Fuller *et al.*, teach or suggest use of an immunosuppressant in combination with the enzyme, nor do Bijvoet *et al.* or Fuller *et al.* suggest that reactivity of the immune system affected the results in any manner. Thus, it would not have been obvious to one of ordinary skill in the art to administer an immunosuppressant in conjunction with the enzyme.

In view of these considerations, the claimed invention would not have been obvious over the teachings of Bijvoet *et al.* in combination with Fuller *et al.*

SUMMARY

As amended, the claims more particularly point out Applicant's invention, specifying that a human individual is treated with GAA periodically, at an administration interval. The reference used in the rejections under 35 U.S.C. 102 (i.e., Fuller *et al.*), fails to teach every aspect of the claimed invention, as it does not teach treatment of a human individual by administration of hGAA periodically at an administration interval, wherein the hGAA is produced in CHO cell culture. Furthermore, the cited references (Bijvoet *et al.* and Fuller *et al.*), when used either alone in the combination indicated in the rejections under 35 U.S.C. 103, fail to render the invention obvious. None of the references, either alone or in combination, teaches or suggests treatment of a human individual having GSD-II, by periodic administration of hGAA at administration interval, wherein the hGAA is produced in CHO cell culture. Furthermore, given

the teachings of the references, one of ordinary skill in the art would not have had a reasonable expectation that disease could, in fact, be successfully "treated" by administration of the hGAA periodically at an administration interval. Thus, the claimed invention would not have been obvious over the cited references. Applicant has, for the first time, demonstrated successful treatment of this genetic disease affecting heart and muscle.

CONCLUSION

In view of these considerations, the claims are in condition for allowance. Applicant's Attorney requests that the Examiner reconsider and withdraw all objections and rejections.

If the Examiner believes that a telephone conversation would expedite prosecution of the application, the Examiner is invited to call Elizabeth W. Mata at (915) 845-3558. If Elizabeth W. Mata cannot be reached, the Examiner is invited to call David E. Brook at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Twice Amended) A method of treating glycogen storage disease type II in [an] a human individual having glycogen storage disease type II, comprising administering to the individual a therapeutically effective amount of human acid α-glucosidase periodically at [a regular] an administration interval, wherein the human acid α-glucosidase was produced in chinese hamster ovary cell cultures.

11. (Amended) The method of Claim 1, wherein the [regular] administration interval is monthly.

12. (Amended) The method of Claim 1, wherein the [regular] administration interval is bimonthly.

13. (Amended) The method of Claim 1, wherein the [regular] administration interval is weekly.

14. (Amended) The method of Claim 1, wherein the [regular] administration interval is twice weekly.

15. (Amended) The method of Claim 1, wherein the [regular] administration interval is daily.

21. (Twice Amended) A method of treating cardiomyopathy associated with glycogen storage disease type II in [an] a human individual having glycogen storage disease type II, comprising administering to the individual a therapeutically effective amount of human acid α-glucosidase periodically at [a regular] an administration interval, wherein the human acid α-glucosidase was produced in chinese hamster ovary cell culture.

22. (Twice Amended) A pharmaceutical composition comprising human acid α-glucosidase, wherein the human acid α-glucosidase was produced in chinese hamster ovary cell culture, in a container [with], the container having a label containing instructions for administration of the composition for treatment of glycogen storage disease type II.